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Chapter: Emmprin (CD147), a Tumor Cell Surface Inducer of Matrix Metalloproteinase

Bryan P. Toole

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CHAPTER 7

Emmprin (CD147), a Tumor Cell Surface Inducer of Matrix Metalloproteinase Production

Bryan P. Toole

Introduction

Emmprin is a member of the Ig superfamily that plays an essential role in several normal tissues but is particularly enriched on the surface of malignant tumor cells in vitro and in vivo. Tumor cell emmprin stimulates production of several matrix metalloproteinases (MMPs) by fibroblasts and endothelial cells, but it also acts in an autocrine fashion to increase MMP synthesis and invasiveness in tumor cells themselves. In addition, emmprin acts as a docking protein for interstitial collagenase on the surface of tumor cells. Increased expression of emmprin in weakly malignant, human breast cancer cells leads to dramatic augmentation of tumor growth and invasion in vivo.

Several important aspects of tumor progression involve proteolytic modification of the pericellular matrix around tumor cells by matrix metalloproteinases (MMPs). For example, MMPs have been implicated in invasion through basement membranes and interstitial matrices, angiogenesis, and tumor cell growth. Strong support for the involvement of MMPs in tumor invasion in vivo comes from experiments in which natural or synthetic inhibitors of MMPs were shown to prevent metastasis in experimental animal models.[1-3] In this chapter I will discuss the function of emmprin, an important regulator of MMP synthesis, in tumor cell invasion.

Emmprin was initially identified as a factor associated with the surface of tumor cells that stimulates synthesis of matrix metalloproteinases by fibroblasts.[4,5] On cloning of emmprin cDNA,[4] it became apparent that emmprin is a member of the Ig superfamily and that it is identical to human basigin[6] and the M6 antigen present on membranes of leukocytes from patients with arthritis,[7] proteins whose functions were not then known. Emmprin is homologous to proteins independently discovered in a wide variety of systems in other species, e.g., mouse gp42 and basigin,[8,9] rat OX47 and CE9,[10,11] and chick 5A11, HT7 and neurothelin.[12-14] Emmprin and its homologs are now also termed CD147. In addition, it is evident that there is a family of molecules related to emmprin. For example, embigin and basigin are closely related,[6] and rat synaptic membranes contain two major Ig superfamily proteins, gp65 and gp55, that are related but not identical to the rat homolog of emmprin.[15]

Tumor Cell Emmprin Stimulates Fibroblast Production of MMPs

A surprising development with respect to MMP production in tumors was the discovery that most MMPs, e.g., interstitial collagenase (MMP-1), collagenase-3 (MMP-13), gelatinase A (MMP-2), gelatinase B (MMP-9), stromelysin-1 (MMP-3), stromelysin-3 (MMP-11), and

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membrane type-MMPs (MT-MMPs), are mainly produced by stromal fibroblasts associated with tumors.[16-20] Moreover, these stromal MMPs contribute significantly to tumor progression in vivo.[20-22] However, MMPs are produced both by stromal cells and by tumor cells, possibly depending on the stage of progression of the tumor, and both sources of MMPs are likely to be important.[17,23,24] Matrilysin (MMP-7) appears to be unique in its restriction to epithelial and carcinoma cells.[17-25]

The almost ubiquitous production of MMPs by stromal cells within tumors, but not within most normal adult tissues, implies that tumor cells may exert regulatory effects on the stromal cells, inducing them to express elevated levels of MMPs. Although it is clear that soluble cytokines and growth factors contribute to this process,[26-28] it is also apparent that tumor cell membrane-bound factors are involved. The first systematic investigation of the latter took place in the laboratory of Dr. Chitra Biswas, where initial experiments suggested that tumor cell-secreted or shed factors were responsible for stimulation of synthesis of MMP-1 by fibroblasts.[29,30] However, subsequent experiments in the Biswas lab showed that most of the MMP-1-stimulatory factor produced by B16 murine melanoma and LX-1 human lung carcinoma cells was plasma membrane-derived, and that this factor could act via direct cell-cell interaction or via shedding of the factor from the cell surface.[31,32] An activity-blocking monoclonal antibody was produced against the factor (originally called tumor cell-derived collagenase stimulatory factor or TCSF)[33] which led to its cloning and full characterization as a transmembrane glycoprotein and member of the Ig superfamily.[4,5] It was also shown to be present in normal tissue[34] and to stimulate production of several MMPs by fibroblasts,[35] and was thus renamed emmprin (extracellular matrix metalloproteinase inducer).[4] (Sadly, Chitra Biswas died in 1993, after having completed the molecular characterization of emmprin).

More recent data has revealed that purified emmprin not only stimulates synthesis of MMPs by fibroblasts but also by endothelial cells. Emmprin stimulates production of interstitial collagenase (MMP-1), gelatinase A (MMP-2) and stromelysin-1 (MMP-3) in both cell types (Refs. 5, 35; Zucker S, Ciao J, Rollo EE, Toole BP, unpublished results). Emmprin-mediated stimulation of MMP-1 synthesis in human lung fibroblasts is dependent on the activity of the MAP kinase, p38, but not ERK1/2 or SAPK/JNK.[36] A recent study has shown that emmprin also stimulates synthesis of membrane-type-MMPs (MT-MMPs) in co-cultures of human glioblastoma cells expressing high levels of emmprin with brain tumor-derived fibroblasts.[37] Both MT1- and MT2-MMP were stimulated in this system. Increased activation of MMP-2 by emmprin has also been observed,[35,37] presumably due to the action of MT-MMPs.[38,39] However, it has been noted that different fibroblast populations differ widely in their response to emmprin;[5,35] the basis for this difference has not yet been elucidated.

The effect of emmprin on tumor cell invasion has been examined in co-cultures of oral squamous cell carcinoma cells and peritumor-derived fibroblasts.[40] In this study the tumor cells were plated on a filter coated with reconstituted basement membrane matrix; the fibroblasts were plated in a well beneath the filter. Tumor cell invasion of the matrix was found to be dependent on emmprin and to result from emmprin stimulation of MMP-2 production, presumably by the fibroblasts.[40]

Autocrine Action of Emmprin Promotes Tumor Cell Invasiveness

Recent data suggest that emmprin acts in an autocrine as well as paracrine fashion. Transfection of weakly malignant MB-MDA436 human breast carcinoma cells with emmprin cDNA leads to an increase in MMP-2 and MT-MMP production (Ref. 41; Caudroy S, Polette M, Nawrocki-Raby B, Toole BP, Zucker S, Birembaut P, submitted for publication). These emmprin-transfected cells were found to be more invasive than vector-transfected controls. Similar findings have been made with the more malignant MDA-435 breast carcinoma cell line without transfection, in that MMP-2 production by and invasiveness of these cells were shown to be emmprin-dependent.[42] In the latter study it was also shown that soluble emmprin inhibits

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between emmprin molecules.[42-44]

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endogenous emmprin action,[42] most likely due to interference with homophilic interactions between emmprin molecules.[42-44]

Emmprin Docks MMP-1 on the Tumor Cell Surface

After synthesis and secretion, some MMPs bind back to the tumor cell surface. For example, MMP-2 binds to either $\alpha v\beta 3$ integrin[45] or to a TIMP2-MT-MMP complex; formation of the latter complex leads to activation of MMP-2.[38,39] A similar mechanism of binding and activation involving MT-MMP may occur with collagenase-3.[46] Gelatinase B can bind to the cell surface via interaction with CD44[47] or a component of collagen type IV.[48] Presentation of MMPs at these docking sites has been shown to promote tumor cell invasiveness.[38,45,47] In a recent study we have shown that, in addition to stimulating MMP production, emmprin is a docking protein for MMP-1.[49] We showed by phage display, affinity chromatography and immunocytochemistry that MMP-1 forms a complex with emmprin on the surface of human lung carcinoma cells. Since collagenase activity is essential for invasion of fibrous tissues,[50] localization of MMP-1 on the tumor cell surface would facilitate this process.

Emmprin Promotes Tumor Growth and Invasion In Vivo

Although it is now apparent that many normal embryonic and adult tissues express emmprin, the level of emmprin expression in tumors, especially malignant tumors, is usually much greater than in corresponding normal tissue.[36,51-55] For example, in one study, the relative distribution of emmprin and gelatinase A (MMP-2) mRNAs was compared by in situ hybridization in normal lung tissue vs squamous cell carcinomas of the lung and in benign mammary growths vs ductal carcinomas of the breast.[52] Emmprin mRNA was detected in all breast carcinomas and the majority of lung carcinomas. Both pre-invasive and invasive cancer cells were positive, but tumor stromal cells and peritumoral tissue showed insignificant emmprin mRNA reactivity. Normal and benign epithelia were negative. MMP-2 and MMP-1 mRNAs, on the other hand, were restricted to stromal cells close to tumor clusters.[36,52] The expression of emmprin mRNA was also analyzed by Northern blots which were then densitometrically scanned; the results showed low expression in normal or benign tissues but high levels at all stages of tumor progression in both lung and breast cancers.[52] Analyses of distribution within tumors made by quantitative image cytometry showed that high levels of emmprin mRNA were expressed in pre-invasive and invasive nests of tumor cells versus low amounts in normal or peritumoral tissues.[52] Both normal and tumor epithelia stained with antibody to emmprin, but expression of emmprin was much stronger in tumor tissue.[53] In other studies, emmprin levels were shown to be higher in transitional cell carcinomas of the bladder than in normal bladder epithelium,[51] and in malignant glioblastomas than in benign gliomas and normal brain tissue.[55] Although emmprin is expressed at a moderately high level in normal non-neoplastic keratinocytes,[34] its presence in oral squamous cell carcinoma is associated with MMP production and tumor cell invasion.[40]

Since malignant tumor cells often express emmprin in vivo and in vitro at much higher levels than normal and benign cells, we recently tested whether over-expression of emmprin stimulates tumor progression.[41] We used human breast carcinoma cells that produce slow-growing primary tumors in nude mice and express relatively low levels of emmprin. We transfected the cells with emmprin cDNA and selected stable transfectant clones with increased expression of emmprin. The emmprin transfectants grew at similar rates to vector-transfected controls in monolayer cell culture. The tumor cells were injected into the mammary fat pad of groups of 10 nude mice in three separate in vivo experiments using different transfectant clones. In all three experiments, the mice injected with emmprin transfectants grew large tumors over a 12 week period whereas controls grew small tumors that were primarily detectable only at autopsy. In addition, the emmprin transfectants gave rise to high levels of MMP expression and to extensive invasion into surrounding abdominal wall muscle whereas controls did not. Mouse survival was markedly decreased with the emmprin transfectants compared to controls.[41] We conclude that increased expression of emmprin leads to increased malignant tumor behavior.

The Functions of Emmprin are Diverse

Recently, a knockout mouse has been produced in which basigin, the murine homolog of emmprin, is lacking.[56] The null mutant is in most cases unable to undergo implantation, possibly due to the involvement of MMPs in this process.[57,58] However embryos that successfully implant and survive past birth have deficiencies in spermatogenesis,[56,59] retinal and photoreceptor development and maintenance,[60,61] other sensory functions,[62] and lymphocyte responses.[62] Any relevance of MMP stimulation to these latter processes has not been established.

Structural analyses have demonstrated that the transmembrane and cytoplasmic domains of emmprin are highly conserved among species, suggesting that these regions are of functional importance. The properties of the transmembrane region also suggest that intramembrane interactions with other proteins are likely to occur.[6,7,10] Emmprin interacts with integrins, $\alpha 3\beta 1$ and $\alpha 6\beta 1$, within the plasma membrane of HT1080 fibrosarcoma cells.[63] It acts as a chaperone for assembly of lactate transporters in the plasma membrane.[64] It binds to cyclophilin A, facilitating HIV virus entry into cells.[65] These interactions are likely to involve the transmembrane and/or cytoplasmic domains of emmprin. Again, however, it is not known whether proteolytic processes stimulated by emmprin are involved in any of these processes. Rather, it seems likely that emmprin has multiple functions, but the underlying mechanisms are presently unknown.

Conclusions

Increasingly, evidence is appearing that firmly establishes the importance of the stroma in carcinoma progression.[66-69] We propose that interactions of tumor cells and stromal cells lead to synthesis and activation of MMPs that in turn promote tumor invasiveness and that emmprin is a crucial component of these interactions. However, emmprin on the tumor cell surface also appears to be directly involved in tumor cell invasiveness, without stromal interactions, by autocrine stimulation of MMP synthesis and by docking of MMP-1 to the cell surface. It is becoming increasingly apparent that tumor cells create a pericellular environment in which many MMPs and other proteases become concentrated, thereby enhancing the ability of tumor cells to invade extracellular matrices and to process locally precursors of factors that promote tumor progression. Emmprin stimulation of MMP production could play a central role in these processes. However, emmprin is also involved in other pathological and physiological events that may or may not involve regulation of MMP synthesis. Whether or not emmprin serves more than one molecular function in malignant tumor cell behavior remains to be seen.

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